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The Production of Convulsions in the White Rat

WILLIAM J. GRIFFITHS, JR.
Psychological Laboratory, Western Reserve University, Cleveland, Ohio

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THE PRODUCTION OF CONVULSIONS IN THE WHITE RAT[1]

WILLIAM J. GRIFFITHS, JR.

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INTRODUCTION

Page (10) has noted that there is some evidence that epileptic attacks in humans may be precipitated by external visual, auditory, or kinesthetic stimuli. This is further confirmed by the history of the seizures and the patients' statement that certain external stimuli tend to bring on the fit. One possible interpretation offered concerning these reflex attacks is that they are associated with specific brain pathology and are of the Jacksonian variety. A second possibility is that they are of the conditioned variety. Experimental induction of seizures in hypnotized epileptics would favor the latter view. With these factors in mind Page attempted to produce seizures in 5 cats and 10 rats. The usual conditioning procedure was followed. Immediately after sounding a bell shocks sufficient to produce a grand mal convulsion were applied to the cortex. Each animal was given one or two trials per day for at least 75 trials. During the course of the experiments many simple reactions were conditioned, but in no instance was a conditioned convulsion obtained. Page points to the loss of consciousness which occurred immediately before the onset of the seizures as the most probable explanation for the lack of success in production of a conditioned convulsion.

On the assumption that excitement is a predisposing factor, or a precipitating factor in convulsions, Page felt that perhaps less current would be needed in the excited condition to produce the reaction. His findings with 10 animals were negative; the same amount was needed.

Maier (7) used keys and air blasts and found that seizures could be produced in rats. His studies were primarily concerned with "conflict." This author has pointed out that, whereas auditory stimulation with air blasts was effective only a few times, the "conflict" situation produced many seizures. Although auditory stimulation was adequate for the production of violently abnormal behavior in some rats, the number of animals having an attack, and the frequency of attacks were increased when "conflict" was introduced into the situation.

Maier (5) has also reported on the relation of behavior, which he has termed "abortive," to the neurotic attack. The rats used in this experiment had each been previously taught to discriminate between negative and positive cards, and each had a record of attacks in the one-window situation. Three situations were used in this experiment. A discrimination test, during which positive and negative cards of the original training series were presented; the one-window situation, in which case the animals were required to jump to a card, irrespective of whether it was positive or negative; the two negative card test. The jumping apparatus hitherto used by this investigator, was modified in this experiment so as to permit the escape of the animal either from the starting box, or by jumping over the stimulus cards. Such a procedure was effective in reducing the seizures, or preventing them. As further evidence of the ability of "abortive" behavior to eradicate the neurotic pattern Maier stated that rats could be caused to have attacks when the old apparatus, which did not provide possibility for such "abortive" behavior, was used. Confronted with the same problem on the new apparatus, "abortive" jumping prevented the seizure. The major conclusions which Maier has drawn from experiments on "abortive" jumping, related to the effectiveness of the latter as a cure for the neurotic pattern.

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[1] The author wishes to acknowledge indebtedness to Dr. A. G. Bills, of the University of Cincinnati under whose direction this work was done in partial fulfillment of requirements for the Ph.D. degree.

Recently Maier (8) has published a report dealing with the permanence of behavior tendencies in "fixated" and non-"fixated" animals. In this report the author referred to metrazol as having a therapeutic effect on abnormal behavior. Maier gave metrazol to animals, obviously for the purpose of determining whether it had any therapeutic value for attacks in psychological tests. He found that metrazol reduced the relative frequency of attacks in the negative card situation. This investigator stated that it was the metrazol, rather than its convulsion, which was the active agent in preventing the seizures.

In another part of the same paper Maier suggested that a non-convulsing dose of metrazol is more disturbing psychologically than a convulsing one. He further suggested that the effect of metrazol seemed to be that of producing a temporary psychological condition that increased the animals' irritability.

In the eighth article of the series entitled, "Studies of abnormal behavior in the rat," Maier, Sacks, and Glaser (8) reported concerning the "Influence of metrazol on seizures occurring during auditory stimulation." It was the stated purpose of the authors to further elucidate the mechanics concerned in the seizure. More specifically, they wished to determine whether the convulsions had a structural or functional basis. Three groups of animals were described. The first group consisted of animals which came from a stock resistant to convulsions, the second group was made up of animals from a convulsive stock, and the third group was composed of rats taken from matings of the first two groups. Animals in Groups 1 and 2 were given a series of metrazol fits until their threshold for the drug was lowered. On the test days they were given a sub-convulsive injection of metrazol and then subjected to auditory stimulation.

The third group of rats received no previous metrazol convulsions before being injected with a sub-convulsive dose of metrazol, and then subjected to auditory stimulation.

Maier found that a large percentage of Groups 1 and 2 could be subjected to seizures by the above procedure, Group 3 did not react so strikingly. From these results the authors felt justified in concluding the previous convulsive seizures with metrazol may increase the tendency of a rat to react to auditory stimulation. The authors offered the further conclusion that auditory fits are functional.

Humphrey and Marcuse (4) found that auditory stimulation by means of door bells produced seizures in 11 out of 23 animals. These workers pointed out that supplementary conditions, such as oscillation of the cage, and previous development of nervous conditions in other test situations, increased the number of animals having seizures.

The abnormal behavior in rats produced by Hall and Martin (3), Humphrey and Marcuse (4), Maier (7), and the Morgans (9), has in general taken the following form: disoriented activity, followed by tonic or clonic convulsions, or both, terminating in a comatose state, during which the rat could be moulded. Gradually these states pass off and the animals apparently return to the normal condition. Hall and Martin (3) have pointed out the similarity of the above pattern to epileptic seizures.

PURPOSE AND METHOD

This paper is concerned with the following questions:

1. Are convulsions evidenced by the white rat in the presence of auditory stimulation actually "audiogenic?"
2. What is the actual role of "conflict" in the production of convulsions in the rat?
3. Is it possible to clearly differentiate convulsive from non-convulsive rats?
4. What effect has continued stimulation over a considerable period of time on onset, duration, and post-convulsive stages of the seizures?
5. Is it possible to produce convulsions without employing auditory stimulation (exclusive of electrically induced seizures)?
6. Corollary to the above, are combinations of two ineffective stimuli effective in producing seizures?
7. What factors may be utilized to alleviate the seizures?

EXPERIMENT 1

Eighteen animals, 8 males and 10 females, were placed individually on the floor of a small room (4′ x 6′). A double coil electric door bell, affixed to a ledge approximately 4′ above the animals' head, was rung for a 3 minute period to induce seizures. Animals were stimulated an average of 91 times during trials spaced at intervals of one day. As table 1 indicates, rat R-6, female, and R-16, male, were stimulated by key jingling, instead of the usual bell.

Rats not succumbing to a seizure after 3′ stimulation were considered negative on that particular trial. No attempt was made to divide animals into "normal" and "convulsive" classes until every rat had received at least 60 stimulations.

The length of time that the bell had been ringing before the animal began the running phase of the fit (running, at first oriented, then "blind" and random, was recognized in the literature and by the experimenter as the first stage of the convulsive pattern), was recorded with a stop watch, and considered as "onset" time. The period actually spent in violent muscular activity was similarly recorded as "duration" of the seizure, and the period immediately following the muscular spasm of the "duration" stage, was recorded as the "post-convulsive" stage. In all cases the bell was discontinued at the close of stage 2 ("duration") of the convulsive seizures. Consequently, stage 3, or the post-convulsive period was considered as extending from the end of stage 2 up to the first voluntary movement on the part of the animal.

EXPERIMENT 2

This experiment was conducted with 10 animals, 6 males and 4 females, using a series of discrimination problems. Each animal was trained on a different discrimination series, designated A-J, consisting of 7 cards. Five of the cards were positive stimuli in the form of circles, the remaining two were negative stimuli. The latter, although identical with each other, were either circles of a given diameter, or a blank card with no circle on it.

For presentation of the stimulus cards in the discrimination series, a modified Lashley Jumping Apparatus was constructed. This consisted of a jumping platform 33″ high guarded on three sides by card board blinds. The fourth side was open and faced the stimulus windows. The two stimulus windows, which held the discrimination cards were square openings 10″ x 10″, cut in an easle 41″ x 36″, and equipped with hinged wooden shutters which could be closed and locked. The top of the jumping stand, on the surface of which the animals were placed, was a square platform measuring 10″ per side. The stimulus windows opened onto a food platform extending the entire width of the easle, and being itself 12″ wide. The surface of the jumping platform, ledges surrounding each stimulus window, and the top of the easle were electrically charged, as was the moveable grid placed on the table, on which the apparatus rested. Current from three dry cells flowed through the system.

Depending on size, animals were required to jump 12–20 cm. (distance of the jumping stand from the stimulus windows could be varied as desired by moving either easle or jumping platform). Training was begun when animals reached the age of 90 days.

Rat BF, a male animal, may be used to illustrate the procedure which was adhered to with all animals used in this experiment. Table 5 may be referred to for clarification of the explanation. From the left side of this table it is noted that Rat BF was trained on discrimination series A. The right side of the same table indicated that the positive cards (cards toward which the rat is to jump) consisted of white circles on a black background. The negative cards were plain black with no figure. The animal was trained to avoid or withdraw from the black card. The "critical" test (test designed to produce "conflict") for this animal was presentation of the black (negative) card in both stimulus windows. The card board blinds fixed to the three sides of the jumping stand, and the grid systems which we have previously described were designed to prevent the animal from escaping from the apparatus during the "critical" test, or during the training periods.

In the case of rat BF the training series began with the largest circle of the 5 which composed the positive stimuli. In successive training periods the diameter of the white circle was diminished until the circle was no longer evident, at which point the rat was forced to face two negative black cards. Incorrect reactions were punished by shock.

The actual training was carried out in the following manner. Previous to the first day of the training period the animal was starved and kept without water for a twenty-four hour period. During the preliminary training period food and water were placed on the ledge behind the stimulus windows. The rat was placed on the jumping stand and the stand moved adjacent to the windows. The animal was permitted to walk back and forth from the jumping platform, through the open stimulus windows to the food shelf. A small amount of food and water was permitted after each excursion. This procedure was repeated until the rat walked readily through the open windows when placed on the jumping platform. One of the stimulus windows was then closed and locked and a negative black card placed in front of the closed shutter. The next several trials consisted in teaching the animal to walk through the open window and avoid the closed shutter, with its black card. The negative black card was placed on the right and left windows in random order to prevent learning of position habits. Food and water from the food shelf was permitted only when the animal went through the open window.

Following the establishment of a definite avoidance response to the negative black card, the animal was ready for presentation of the first positive card of the discrimination series. In the case of rat BF, this card contained the white circle with the largest diameter of the 5 in its series (A). This card was referred to as circle range 1, positive.

At this point we shall digress for an explanation of the terminology used with reference to the stimulus cards composing a discrimination series. The discrimination problems consisted of a series of circles painted on card board squares, of a size permitting insertion in the stimulus windows, or on a closed shutter of a stimulus window. Discrimination problems were grouped into series A-J, dependent on the color of the circle, and the background on which it was painted. For example, series A (table 5) contained discrimination cards composed of white circles on a black background. Series B consisted of black circles on a white background, etc. Each series contained 7 discrimination cards. In the event that a card contained a circle on it, reference was made to it by range, which indicated the diameter of the circle. For example, circle range 1, referred to the first discrimination card on which the animal was trained. Depending on the particular training series, range 1 could indicate either the largest of the smallest circles of the series. In any event, the rest of the circles composing the series progressed or regressed in their ranges, from that of circle range 1, toward the negative card. As mentioned, circle range 6 was identical with the negative stimulus.

Reference may be had to the right side of table 5 in clarifying the above description. We note from this table that series A consisted of white circles on a black background for the positive stimulus, and a plain black card for the negative member, this indicates regression in the ranges of circles 1–5. Since the black card is the negative member, and since the sixth card of any series is identical with the negative member of the series, hence the discrimination cards included in series A vary from a large white circle (range 1) through 4 intermediate ranges to a plain black card (card 6).

Discrimination series I, B, D, F, and E (table 5) follow this regression from range 1 to range 5, from large to small diameter circles. Conversely, discrimination series C, G, H, and J, progress from the smallest diameter at range 1 to the largest at range 5. Range 6, being the equivalent of a negative card, was thus the largest circle of the series.

We return now to rat BF, which we were using as an illustration of the method of training animals used in this experiment. After having established a withdrawal response to the negative stimulus (black card), by the procedure outlined, the first positive card was leaned against the open window (circle range 1, series A). In the training of BF the card with the large white circle on a black background was leaned against the open window in such a way that the animal could walk from the jumping platform to the food shelf by merely pushing over the card with the white circle on it. Positive and negative cards were, of course, shifted at intervals to avoid position habits from becoming established. After the animal had correctly differentiated positive circle range 1 from the negative black card several times, the positive card was fitted snugly into one window, the negative card similarly placed in the remaining window, and both window shutters were raised. The jumping stand was moved back to a distance of approximately 21 cm. from the easle windows. This point marked the close of the preliminary training period, which, as we have seen, served to acquaint the animal with the apparatus and to establish the approach-withdrawal reactions to their proper stimuli. The animal was replaced in its cage, starved and kept without water for twenty-four hours.

Following the rest and preliminary training periods, the rat entered upon training day 1. Using again the circle range I as the positive card toward which the rat was to jump, and the plain black card as the negative stimulus, from which the animal was to withdraw, BF received 28 trials at 10 A.M., 4 trials at 2 P.M., and 30 trials at 3 P.M. The positive and negative cards were presented in random order to prevent the formation of position habits. Food and water in small quantity were permitted only when correct reactions were made. It may be mentioned that the animals seemed to perform the discrimination reactions as a type of "trick" after they had learned what was expected of them, and ate very little, even following a starvation period. Occasionally pushing, tapping, or a slight shock was necessary when the animals exhibited signs of lethargy or negativism.

On training day 2 (following immediately training day 1 with no starvation period) an identical procedure was followed using again circle range 1 as the positive card, and the plain black card as the negative stimulus. On day 3 the rat was again left in the living cage without food or water. Training days 4 and 5 were repetitions of the procedure recorded for days 1 and 2, with the exception that positive circle range 2 replaced positive circle range 1. The rat was left in its cage on day 6 without food or water. Training days 7 and 8 were repetitions of the procedure indicated for 1 and 2, and 4 and 5, with the exception that positive circle range 3 replaced positive circle range 2, used on days 4 and 5.

Training days 10, 11, 13, and 14, and starvation days 9, 12, and 15, followed in due order. Each two training days saw a change in the positive circle to approach the negative card. In the case of rat BF, under consideration, this would mean that the smallest diameter circle of discrimination series A was presented on day 14.

When the animal had mastered the discrimination of this small diameter circle from the black card, we were ready to prepare the rat for the "critical" test with the two black cards. Prior to presentation of the two negative cards, the animals were given intensive re-training (on consecutive days) on circles ranges 1–5 which they had been trained on previously. In accordance with this procedure, BF was starved and kept without water on day 15, and on the following day (16), was re-tested with positive circle range 1 and the negative black card; which, as will be noted, was the same procedure as carried out on training days 1 and 2. On such re-test days the rats were given 52 trials distributed throughout the day as follows; 20 trials at 10 A.M., 2 trials at 2 P.M., and 30 trials at 3 P.M. On days 17, 18, 19, and 20, 52 trials were given, re-testing the animals on all five ranges of the positive card opposed to the negative.

On day 21, the rats were faced for the first time with a negative card in each stimulus window. Immediately preceding this exposure, animals were given a preliminary test of 20 trials on circle range 5 with the negative card. The animals' reactions to presentation of the two negative cards were carefully recorded, and no electric shock applied. On day 22 the procedure outlined for day 21 was repeated and in addition the electric shock was applied to the rat. Again the animals' reactions were recorded. Day 23 was a rest-starvation period and the rats were kept in the living cages without food or water. On training day 24, the animals as usual were given the preliminary 20 trials on positive circle range 5, and then faced with the two negative cards, without electric shock. Day 25 was a starvation period, and on day 26 the usual procedure was repeated, this time with the electric shock.

This procedure was continued as outlined with all animals until they had 15 exposures to the two negative cards; shock was used on alternate days.

EXPERIMENT 3

This experiment was referred to as Production of Convulsions by "Sensitization." The subjects were 19 male and 17 female rats. We wished to determine whether animals, whose histories indicated only a very small percentage of seizures when subjected to bell stimulation, would exhibit an increased percentage of convulsions when the rather ineffective bell stimulation was combined with another equally ineffective stimulus.

The 36 animals were divided into two major groups. Animals in the first group received sub-convulsive doses of metrazol as the "sensitizing" agent before being stimulated with the bell. Rats in the second group were subjected to stimulation obtained from beating on a strip of galvanized iron, in combination with bell ringing.

Group 1 (F_1 animals) was further divided into 3 sub-groups, (table 6) on the basis of genetic histories. All parental animals of this group were non-convulsive. The offspring of these animals (F_1 used in this experiment) had themselves only a very low percentage of seizures when stimulated with the bell alone, and none at all when subjected to the sound of striking on a galvanized tin strip. This group was composed of 6 males and 2 females. Sub-group 2 consisted of 9 animals, 4 males and 5 females, F_1 generation of parents, one of which was convulsive and the other non-convulsive. Procedure for administration of metrazol was the same for all three subgroups and was carried out as follows: all rats were first stimulated for 5 minutes with the bell. Failing to succumb to a seizure, the animals were given sub-convulsive doses of metrazol (table 6). After injection, an interval of 15 minutes elapsed before the rats were again subjected to bell stimulation (not in excess of 5 minutes) and the results recorded in table 6.

Group 2 was composed of 17 rats. Of these, 6 were males, and the remainder females. The experimental procedure was, in general, the same as that used with Group 1, with the exception that the animals were stimulated by beating with a stick on a galvanized iron strip during the ringing of the bell (in place of metrazol injections). These animals were all given pre-tests to determine the effectiveness of "extra noise" and electric bell, presented separately, in inducing seizures. In no case was the "extra noise" alone effective. In a few cases the bell alone was effective a small percentage of the time (table 7).

EXPERIMENT 4

From observations made during experimentation with stimulation of the rats with an electric bell to obtain convulsive seizures, we designed an experiment to investigate the possibilities of psychological means of alleviating the seizures. We had observed that animals, which, during the "oriented" stage of running, occurring as part of the pattern of a typical seizure (cf. Discussion) succeeded in "hiding" behind the photographic curtain, or wedging themselves into a crevice in the card board retaining wall, guarding the stimulus area, never had a convulsive seizure.

An apparatus was constructed to incorporate this "shelter" factor, for the purpose of determining its value in alleviating the convulsions. We selected 12 rats, 5 males and 7 females, from amongst the convulsives produced in Experiments 1 and 3, to be tested in the "shelter" situation. The animals were placed in a galvanized iron cylinder with the stimulus bell hanging 4′ above their heads. The cylinder enclosed an area of 20″ on the floor, where the animals were placed for stimulation. One one side of the galvanized enclosure a 3″ x 5″ opening was cut, level with the bottom of the cylinder. This opening could be closed at will by a shield, operated from outside the enclosure by the experimenter. The 3″ x 5″ opening led to an open run-way, 3′ x 1′, ending in an experimentally constructed "rat-hole." The latter was constructed by splitting two ordinary galvanized iron pipes, bolting them together and covering the open top with wire netting. The pipes thus formed a space of about 10″ within which an animal could "hide." The distance from the bell to the center of the "rat-hole" was approximately 4′ (equal to the distance of the bell from the center of the galvanized cylinder). The experiment with this "shelter" apparatus was carried out in the following manner: the rat was placed in the iron cylinder and the bell turned on. At a given point in the "oriented" running stage of the convulsive pattern, the experimenter removed the shield, thus exposing the opening in the galvanized cylinder. The number of times that the rat took advantage of the altered environment and ran through the 3″ x 5″ hole, along the runway and into the "rat-hole," was recorded. The number of seizures exhibited by animals making this "shelter" reaction was also recorded.

Corollary to the above experiment, 3 female and 1 male animal were selected from the convulsives used in Experiment 1, to serve as subjects in the "binding" experiment. This experiment was conducted in the following manner: the rats were rolled up in bandage cloth with the head and ears protruding. The cloth was kept in place by two bonds in the vicinity of the fore and hind limbs. Animals thus restrained were held 4″ from the ringing bell. Three of the four subjects were anesthetized prior to the binding to negate struggling reactions. Suitable time, of course, elapsed between the period of anesthesia and the stimulation. Following exposure to auditory stimulation, the animals were unbound and placed in a previously learned maze ("closed" type), to indicate the presence or absence of a refractory period, which ordinarily follows a convulsive seizure.

Both "shelter" and "binding" experiments were presented a number of trials, equal to the total number of times the animal was stimulated in the absence of these conditions (cf. total stimulation in tables 1 and 7). In cases of rats from Experiment 3, which were used in the "shelter" experiment, the "sensitizing" combination was employed as stimuli, not merely the bell alone.

RESULTS OF EXPERIMENT 1

From table 1, we note that the rats may be divided into general classes of convulsive and non-convulsive. Certain animals, namely, RX, R-12, R-LHL, and R-BW, however, cannot definitely be classed in either of the above categories. Although the percentage of seizures in the above animals was small, as the table indicates, yet, due to the presence of these convulsive tendencies it would be misleading to class these animals as non-convulsives. Table 4 indicates the importance of prolonged test periods in determining the convulsive tendencies of rats. Rat RX, for instance, never showed any signs of a seizure until the 57th trial, thereafter, as the table indicates, it had seizures 4 per cent of its trials. Excluding the border line cases mentioned above, we have considered rats 6, 16, 18, 72, 14, S-SC, L-AS, RA, and R-FF, definitely convulsive. Animals R-71, R-BW, R-LE, RB-2, and R-RE, were considered non-convulsive.

Table 2 indicates the effect, on the speed with which a convulsion may be induced, of continued stimulation of animals over a long period of time in the absence of prolonged rest periods. It may be pointed out that we found no evidence of any adaptation to the stimulation in the way of disappearance of seizures, in fact, the results expressed in table 2 point toward the opposite conclusion. Without exception, the average onset time for a given rats' last 10 seizures was less than that necessary for the same animals' first 10 seizures. As the table indicates, the per cent difference in time necessary to elicit a seizure, in the first and last 10 seizures, varied from 3 to 64 per cent, in favor of less stimulus for the last 10 seizures.

TABLE 1

Total stimulations and seizures

RAT	SEX	TOTAL STIMULATIONS	TOTAL SEIZURES	PERCENTAGE SEIZURES	STIMULUS
R-6	♀	60	54	90.0	Keys
R-16	♂	75	62	82.6	Keys
R-18	♀	65	55	84.6	Bell
R-72	♂	103	73	70.8	Bell
R-14	♀	108	77	71.3	Bell
R-X	♀	100	4	4.0	Bell
R-71	♂	75	0	0.0	Bell
R-B2	♂	100	0	0.0	Bell
S-SC	♂	100	65	65.0	Bell
L-AS	♀	60	35	58.3	Bell
R-LHL	♀	70	3	4.3	Bell
R-LE	♀	70	0	0.0	Bell
R-BW	♀	209	10	4.8	Bell
R-FF	♀	105	74	70.4	Bell
R-BW	♂	100	0	0.0	Bell
R-RE	♂	72	0	0.0	Bell
R-12	♀	75	5	6.0	Bell
R-A	♂	100	78	78.0	Bell

TABLE 2

Average time of onset in first ten seizures compared with average onset time in last ten seizures

RAT	SEX	ONSET OF FIRST TEN SEIZURES	ONSET OF LAST TEN SEIZURES	DIFFERENCE IN ONSET TIME BETWEEN FIRST AND LAST TEN SEIZURES	PER CENT DECREASE IN SEIZURE TIME OF LAST TEN SEIZURES
		seconds	*seconds*		
R-6	♀	100.6	93.7	6.9	7%
R-18	♀	54.4	31.1	23.3	43%
R-14	♀	22.4	17.8	4.6	20%
L-AS	♀	42.0	30.9	11.1	26.4%
R-A	♀	29.3	10.4	18.9	64%
R-FF	♀	52.4	23.9	28.5	45%
R-16	♂	42.7	21.1	21.6	50%
R-72	♂	52.3	21.3	31.0	59%
R-SSC	♂	81.8	79.2	2.6	3%

Conversely, table 3 shows that prolonged, continuous stimulation of convulsive animals leads to an increase in the amount of time spent by the animals in the post-convulsive, or coma-state, following a seizure. Without exception, the average number of seconds spent in the abnormal behavior. following cessation of the stimulus bell, was greater during the last 10 seizures, than was this same period during the first 10 convulsions. As table 3 indicates, the per cent differences between the average post-convulsive periods of the first and last 10 seizures, were uniformly high, in most cases above 50 per cent. Rat R-18 was the only exception to this statement.

TABLE 3

Average post-convulsive period of the first ten seizures compared with that of the last ten seizures

RAT	SEX	AVERAGE DURATION OF THE POST CONVULSIVE PERIOD IN FIRST TEN SEIZURES	AVERAGE DURATION OF THE POST CONVULSIVE PERIOD IN LAST TEN SEIZURES	DIFFERENCE	PER CENT INCREASE IN DURATION OF POST CONVULSIVE PERIOD IN LAST TEN SEIZURES
				seconds	
R-6	♀	29.4	46.3	16.9	57%
R-18	♀	31.2	36.4	5.2	16%
L-AS	♀	28.9	57.3	28.4	97%
R-A	♀	73.4	152.9	79.5	108%
R-FF	♀	56.0	129.9	73.9	131%
R-14	♀	22.2	42.8	20.6	94%
R-16	♂	48.0	73.5	25.5	53%
R-72	♂	28.0	43.2	15.2	54%
R-SSC	♂	21.5	52.0	31.5	141%

TABLE 4

Percentage of seizures obtained in animals with delayed onset

RAT	SEX	TRIALS IN WHICH FIRST SEIZURE OCCURRED	TOTAL NUMBER OF SEIZURES	TOTAL NUMBER OF TRIALS	PER CENT OF SEIZURES
R-X	♀	57th	4	100	0.04 ± 0.019
R-12	♀	21st	5	75	0.06 ± 0.027
R-BW	♀	8th	10	209	0.048 ± 0.014
R-LHL	♀	14th	3	70	0.043 ± 0.024

RESULTS OF EXPERIMENT 2

The results of our attempt to produce convulsions by the so-called "conflict" method were uniformly negative, with one exception. The most common reaction to presentation of two negative cards in the absence of shock was withdrawal. When shock was added in the presence of two negative cards the animals' reactions were variable. In some instances the rats would exhibit marked signs of emotionality when the two negative cards were presented. In other cases, emotional behavior was evidenced only when the shock was applied with the negative stimuli. With other animals no emotionality was evidenced either with the negative cards plus shock, or negative cards alone; rather these animals seemed to manifest a general negativism. For a clearer picture of the actual results obtained in Experiment 2, excerpts from our original records may prove helpful. Table 5 may be consulted for additional information. As the table indicates, rat BF made 733 correct reactions to the discrimination problems presented him (possible 823 correct reactions could be made). Column 5, table 5 indicates that this animals' reaction to two negative stimuli was not a convulsize seizure. Similarly, application of the electric shock in combination with negative cards failed to produce a seizure. Consulting our original records on rat BF, we find the following notations regarding its behavior.

4/21/40. "Animal (rat BF) faced for the first time with two negative cards. Rat walks to the far edge of the jumping stand. Neck stretched toward the stimulus cards. After a brief period in this situation, animal backs up slowly, pressing himself against the side walls of the jumping stand and remaining motionless for the remainder of the period. No clear or marked signs of emotionality. Respiration apparently normal, slight movements of the vibrissae."

TABLE 5

Record of production of convulsions by "conflict" situation

SERIES	RAT	SEX	CORRECT REACTIONS	REACTIONS TO NEGATIVE CARD	REACTION TO SHOCK PLUS NEGATIVE CARD	SERIES	POSITIVE CARD		NEGATIVE CARD		Direction
							Back-ground	Circle	Back-ground	Circle	
A	BF	♂	733	–	–	A	black	white	black	none	regress
C	BT	♂	765	–	–	C	black	gray	gray	none	progress
E	BH	♂	623	–	–	E	BW	large BW	BW	small BW	regress
G	BM	♂	554	–	–	G	white	small CH	white	large CH	progress
I	BX	♂	576	–	–	I	white	large VH	white	small VH	regress
B	BE	♀	569	–	–	B	white	black	white	none	regress
D	BS	♀	574	–	–	D	BW	gray	BW	none	regress
F	BA	♂	595	–	+	F	gray	large white	gray	small white	regress
H	BL	♀	662	–	–	H	gray	small black	gray	large black	progress
J	BZ	♀	694	–	–	J	white	small HB	white	large HB	progress

Key: BW = black and white; CH = cross hatched; VH = vertical hatched; HB = half black.

4/26/40. "Rat BF races to the front of the jumping platform when two negative cards are presented. At this point electric shock is applied for a brief interval. Animal jumps slightly and begins "weaving" movement of the head. Respiration appears to be considerably increased. Audible teeth chattering. This type of behavior continued for approximately 4′30″. Animal then starts to the back of the stand. At this point shock is again applied. Animal quickly returns to the front of the platform and repeats 'weaving' movement."

5/10/40. "Negative cards presented to rat BE. Animal goes to the front of the jumping stand; leans far out wavers from one side to the other; teeth chattering clearly audible. Animal retreats to the middle of the jumping stand, paces from one side to the other. This reaction lasted approximately 5′30″. Animal then retreats to the back of the jumping stand and remains motionless for the rest of the test."

5/12/40. "Negative cards presented rat BE. As the animal starts toward the side wall of the jumping platform, shock of brief duration is applied. Animal 'vocalizes,' respiration increases markedly, eyes protrude. Tail is partially lifted free of the ground, and the rat begins to hurry back and forth on the front of the jumping stand. Occasionally the animal stops this kind of behavior and engages in 'head weaving.' This reaction is continued for approximately 7′32″, following application of the shock. As the animal started again for the back of the jumping platform, shock applied the second time. Rat raced to the front of the jumping platform, 'vocalizing' even after cessation of the shock. Rat remained on the edge of the stand leaning toward the stimulus windows and 'weaving' the head."

6/16/40. "BT presented two negative cards. Begins 'weaving' motion of the head. Animal then turned its back to the stimulus windows and pressed itself against the side walls of the jumping platform. Rat stayed in this position ignoring the stimuli."

6/17/40. "BT begins 'weaving' motion of the head when two negative cards are presented. At this point while the animal is fairly close to the front of the jumping stand shock is applied. Violent respiration is at once evident. Vibrissae move rapidly, slight eye 'bugging' is noted. Movement to and fro on the edge of the jumping platform increases, as does the rapidity of the head movements. Reaction continues 2′14″ after the shock is given. Following this activity the animal returns to the front of the jumping stand and sits motionless facing the two negative cards. Respiration and vibrissae movements normal. Shocked again in this position, the animal emits a 'squeal' and runs to the edge of the jumping stand, repeating the above reactions."

The above excerpts give a general idea of the type of reaction obtained from using the negative cards alone, and in combination with an electric shock, as a means of producing convulsions. As table 5 shows, rat BA, a male animal, trained on discrimination series F, showed the only exception to the type of reaction recorded above. This animal, as indicated in Column 6, table 5, succumbed to a convulsive seizure on presentation of the two negative cards in combination with an electric shock. Our records read as follows concerning this rat:

4/19/40. "Upon presentation of two negative cards, animal BA commences quick circular turns. Violent increase in respiration, eye 'bugging,' twitching of the vibrissae indicates increased emotionality. Attempts are made by the animal to escape from the jumping apparatus. Reaction lasted 5′38″. Animal then retreated to the center of the jumping apparatus, apparently disregarding the negative stimuli."

4/20/40. "Animal BA gives evidence of great excitement when the negative cards are presented. Subsequently rat appears to become acclimated and starts to the rear of the jumping stand. At this point the electric shock is applied. Signs of excitement increase. The animal jumps to the top of the easle, shocked again, jumps to the table top. Shocked on moveable grid; jumps to the floor, begins to run in wide circles, blindly, culminates in a convulsion lasting 17′30″; complete pattern."

Twelve such reactions were obtained from this animal out of fifteen exposures to shock plus negative cards.

RESULTS OF EXPERIMENT 3

The results of administration of sub-convulsive doses of metrazol, combined with auditory stimulation, as a method of producing convulsions in refractory animals, is indicated in table 6. It is evident on examination of this table that the method was most effective with animals whose parents were both convulsive. Conversely, the method proved least effective in animals, neither of whose parents were convulsive. Judging from the seizure percentages following injections of metrazol, recorded in the last column of table 6, it appears that animals which are the offspring of one convulsive and one non-convulsive parent show the most variability regarding the effectiveness of metrazol as a "sensitizing" agent.

TABLE 6

Production of convulsions by metrazol sensitization in animals of the first generation

RAT	SEX	WEIGHT	PARENTAL HISTORY	PREVIOUS TRIALS	PER CENT SEIZURES	NUMBER OF INJECTIONS	AMOUNT INJECTED	PER CENT SEIZURES
		grams					*mgm.*	
RS	♂	339–472	–	35	0%	45	30–80	2%
RB	♀	200– 61	–	30	0%	43	40–50	2.3%
RF	♂	198–301	–	30	0%	43	30–70	13.0%
RB	♂	125– 67	–	30	0%	21	20–30	0%
RLE	♂	204– 68	–	33	0%	37	30–50	8%
RS	♀	197–211	–	39	0%	10	20–30	0%
RF	♂	154–253	–	26	0%	36	20–50	2%
RH	♂	200–348	–	32	3%	31	30–70	6%
RT	♂	200– 53	+	26	46%	19	10–30	54%
R2T	♀	174–303	+	26	0%	53	30	73%
R2B	♀	198–201	+	29	0%	43	20–30	63%
RT	♀	130–63	+	38	0%	34	20–40	70%
RRE	♀	264– 73	+	56	0%	27	30	100%
R2E	♀	153– 86	+	56	0%	26	30	83%
RB	♂	169–251	+	20	0%	22	30	74%
RLE	♂	127–314	+	20	0%	38	20–40	50%
RH	♂	324– 41	+	34	60%	29	50	79%
BF	♀	210– 53	±	88	0%	25	30–40	28%
BWT	♂	249–328	±	50	0%	20	40–50	0%
RA	♂	342– 65	±	40	0%	28	50	75%
R2S	♀	158– 93	±	333	3%	25	20	33%
RBW	♂	322– 48	±	50	4%	26	30–50	0%

With two exceptions (R-6 and R-3, table 7) combination of two stimuli, in the form of bell ringing and beating on a galvanized tin strip with a wooden mallet, proved more effective in inducing seizures in previously refractive animals, than was the case when one stimulus only was used. This fact is evident by comparison of seizure percentages prior to addition of extraneous noise, recorded in Column 5, table 7, with those following addition of the "sensitizing agent, recorded in Column 6 of the same table. Considerable variability as regards the reactions of individual animals to the sensitizing agent, used with Group 2 in Experiment 3, is noted in table 7. Extraneous noise in combination with the auditory stimulation obtained by bell ringing, is no more effective in producing seizures in rats 3 and 6, than was the bell alone. In the case of rat 14, the combination of stimuli proved only slightly more effective than the bell itself. This was likewise true of rats 12, 15, and 16. The remaining animals, rats 1, 2, 5, 8, 10, 11, 13, and 17, however, showed considerable increase in the percentage of seizures following addition of extraneous noise as a sensitizing agent.

TABLE 7

Production of convulsions by auditory sensitization

RAT	SEX	AGE AT TREATMENT	PREVIOUS TRIALS	PER CENT SEIZURES	PER CENT SEIZURES AFTER SENSITIZATION	DIFFERENCE	$D/\sigma op$*
		days					
R- 1	♂	121	23	0.13	0.35	0.22 ± 0.122	1.80
R- 2	♀	121	25	0	0.75	0.75	
R- 3	♀	152	25	0	0	0	
R- 5	♂	120	25	0.36	0.70	0.34 ± 0.131	2.59
R- 6	♀	130	27	0	0	0	
R- 8	♀	124	26	0.23	0.80	0.57 ± 0.260	2.19
R-10	♀	140	29	0.27	0.60	0.33 ± 0.122	2.70
R-11	♂	139	29	0.20	0.70	0.50 ± 0.112	4.46
R-12	♀	134	28	0	0.04	0.04	
R-13	♂	120	25	0	0.50	0.50	
R-14	♂	135	28	0	0.01	0.01	
R-15	♀	120	25	0	0.02	0.02	
R-16	♂	130	27	0	0.05	0.05	
R-17	♀	125	26	0	0.75	0.75	

* Based on standard error.

RESULTS OF EXPERIMENT 4

Table 8 indicates the effectiveness of the "shelter" reaction as a method of reducing the percentage of seizures in convulsive rats. Column 3 shows the percentage of convulsions succumbed to by the rat previous to the introduction of the "shelter." Column 4 indicates the percentage of times that a given animal took advantage of escape possibility and ran to the "rat-hole." The fifth column shows the percentage of convulsions experienced by animals notwithstanding the "shelter" reaction. A glance at Column 6 of this table is sufficient to indicate the effectiveness of this psychological method of reducing percentage of convulsions. As is noted, this last column shows the difference in percentage between pre- and post-"shelter" reactions. Without exception, seizure percentages are reduced on an average of 57.8 per cent, by addition of the "shelter."

Table 9 merits little explanation. Without exception, binding alleviates convulsive seizures. Also, without exception, bound animals showed no refractory period when placed in a previously learned "closed" maze. The animals ran this maze without error or delay, a fact not characteristic of rats experiencing a convulsive seizure.

TABLE 8

Effectiveness of "shelter" in alleviating convulsions

RAT	SEX	PER CENT SEIZURES	PER CENT ADIENT RESPONSES TO SHELTER	PER CENT SEIZURES AFTER SHELTER	DIFFERENCE
R-6	♀	90%	40%	10%	80%
R-16	♂	82.6%	35%	15%	67%
R-18	♀	84.6%	62%	21%	63.6%
R-72	♂	70.8%	70%	25%	45.8%
R-14	♀	71.3%	20%	0%	71.3%
R-2	♀	75%	32%	15%	60%
R-5	♂	70%	50%	25%	45%
R-8	♀	80%	25%	0%	80%
R-10	♀	60%	90%	38%	22%
R-11	♂	70%	40%	12%	58%
R-13	♂	50%	30%	3%	47%
R-17	♀	75%	65%	20%	55%

TABLE 9

Effectiveness of binding in alleviating seizures

RAT	SEX	PER CENT SEIZURES	PER CENT SEIZURES WHEN BOUND	PER CENT CLOSED MAZE REFRACTORY
S-SC	♂	60%	0%	0%
L-AS	♀	58.3%	0%	0%
R-A	♀	78.0%	0%	0%
R-FF	♀	70.4%	0%	0%

DISCUSSION

A point of major controversy in the general field of production of convulsions in the rat has centered around the so-called "audiogenic" as opposed to "functional" points of view regarding causation of fits manifested by some rats subjected to auditory stimulation. Another factor concerning which there is considerable lack of agreement relates to the role of "conflict" in production of seizures.

Investigators at Queens' College (4) feel that it is unlikely that any convulsive seizures could be produced without the factor of "conflict."

Maier (7) definitely feels that, of the components air-blast and negative card situation, which form the convulsive producing stimuli employed in his investigations, the latter is of far greater importance than the former.

Morgan (9) states that, "... it is certain in our case that the abnormal behavior is connected with the auditor component of the air blast directly."

In addition to the above mentioned factors, our work with metrazol, given refractory animals in sub-convulsive doses, and Maier's recent publication of results obtained with sub-convulsive doses of this drug, makes it necessary to generally clarify the role of metrazol in production of convulsions in the white rat.

We first draw attention to Experiment 1 (table 1) wherein 18 rats were stimulated with a bell in order to obtain convulsive seizures. It should be noted that no attempt was made to divide these animals into convulsive and non-convulsive until each had a minimum of 60 stimulations. Our stimulation period of 3′ was likewise longer than that of most workers with the exception of Humphrey and Marcuse (4). Maier, for example, differentiated "neurotic" from "normal" rats on the basis of a two minute stimulation period over five successive days. Animals selected by this investigator as abnormal were those exhibiting convulsions on any one of the above test occasions. As we have previously indicated, in dealing with the results of Experiment 1, such a procedure admits the possibility that a number of Maier's so-called "normal" animals were actually susceptible to convulsive seizures and would have exhibited the reaction had they been tested over a longer period of time. The initial failure to differentiate the two types of animal would naturally vitiate any conclusions drawn from future experiments with these rats. This would be especially true as regards the study of the heritable factor of the seizures. The above mentioned failure is perhaps the explanation of Maier's statement that, "the convulsive pattern is not completely accounted for in terms of heredity."

As an example of the necessity of more preliminary tests on animals which are to be used in experiments on abnormal behavior, we mention the case of rat BW. Stimulation of this animal over a period of one year, led to 50 per cent seizures, whereas the percentage after the first nine trials was only 20. We also point out that the same animal may change the pattern of its convulsive seizures so that we cannot speak of "typical" patterns without having adequate records on each individual rat.

In experimenting with the bell as a means of inducing seizures we made several observations leading to the formulation of the work reported under Experiment 4 in the preceding sections of this paper. These observations in conjunction with the results reported on the "shelter" reaction may clarify the disputed question previously mentioned concerning the causation of seizures attending auditory stimulation. We employ the term "audiogenic" as indicating that an auditory stimulus itself, acting as a sort of "electric" generator, "touches off" a convulsion. In as much as our results have indicated (cf. Experiments 2 and 3) that convulsive seizures may be produced in instances where the auditory stimulation is distinctly subordinate, or not required at all, the question at issue is, in cases where auditory stimulation is used exclusively for eliciting a seizure, are the attendant convulsions actually "audiogenic" in the sense of the definition of this word given above?

The "affective" tone of animals under bell stimulation was one of the first factors which impressed us. Susceptible animals appeared "scared to death." Such rats appeared to be vainly trying to escape from a highly undesirable and frightening stimulus in the form of the ringing bell. The shaking, running, teeth chattering, etc., observed in animals used in Experiment 1, seemed to indicate a general fear reaction.

Some animals seemed to find an outlet for their nervous energy by engaging in violent face-washing behavior, backing against the corners of the room, flattening against the wall, hiding behind the photographic curtain, or wedging themselves into a crevice in the card board retaining wall. Animals making such reactions never had a seizure. In the event that the animals were forced into the center of the room where all kinesthetic sensations were lacking many evidenced convulsive seizures. Observing such reactions it seemed very unlikely that the nature of the stimulus could in itself be an adequate explanation for the presence or absence of convulsive seizures, since the source of stimulation remained at practically the same distance from the animal regardless of whether it was in the center of the room, or wedged behind one of the above mentioned "shelters." The above observations led to the experiments on the "shelter" reaction, and the "binding" of animals reported in the preceding sections. From the results of these experiments, i.e. the effectiveness of "shelter" and "binding" in alleviating convulsions, it would seem that the "affective" tone of the animal is altered depending on whether he is in an open or sheltered field. This affective disposition would then be paramount in importance for determining whether a given animal would succumb to a seizure when stimulated with the bell. Narrow enclosures, such as those formed by galvanized iron cones, are said to be more effective in producing seizures than are larger spaces. The lack of adequate feelings of "security," aroused perhaps by pressure sensations, in the unprotected field formed by the galvanized iron, is a possible explanation of the superiority of a small enclosure over a larger area in producing seizures.

Another observation made by us, which we feel throws doubt on the validity of the "audiogenic" theory as an explanation of the phenomenon of convulsions in the rat, is the considerable variability of the seizures. An animal which succumbed to a seizure on Monday may not do so on Tuesday or Wednesday. It is difficult to conceive of the auditory system itself varying so considerably as regards susceptibility to the same stimulus.

As table 9 has indicated, convulsive rats exhibit neither seizures, nor the after-effects of fits, when wrapped in a cloth and held under the bell. Such animals certainly received no different auditory stimulation (being kept the same distance away from the source of the auditory stimulation as when in the center of the field) yet the "closed" maze retention test indicated no refractory period, characteristic of animals recovering from a convulsive seizure. If the "audiogenic" theory is correct, it is difficult to see why such animals give no evidence of having experienced a seizure. We believe that it is not out of the question to conceive the bound animals as being affectively in a different condition from the rat, which in its terror is vainly attempting to escape from the fear-provoking stimulus. This is evidenced by the initial running period, which at first appears to be quite oriented, as noted by the fact that the animal directs its efforts toward the corners of the room, where possible escape might be accomplished. Failing to find an outlet, the oriented running stage passes into the blind, probably "unconcious," wild, thrashing about the enclosure. This stage is followed by the actual spasm or seizure, composed of tonic and clonic convulsions, ending in coma-like rigidity. The bound animal may be just as much afraid as the free running individual in the presence of the bell; yet his "affective" condition may be more like the individual "paralized" with fright, rooted to the spot, incapable of moving, and still in full possession of his "mental" processes.

We may, of course, dispense with the term "fear" used in the above discussion, and substitute "emotionality." This is a concession to those individuals who object to the use of terms such as "conciousness" and "fear" when speaking of emotional reactions in animals. Of the various types of emotions we are familiar with, and from close observation of the reactions of the animals to auditory stimulation, it is our opinion that "fear" is the proper term to use referring to these animals. If we ignore the "affective" tone of the rats, or deny that such a term has meaning when applied to these animals, then we must either make our terminology more general, and more vague, or else assume that not only does auditory stimulation itself contain a convulsion producing factor, but also that it has a factor which produces running. We have observed that in all cases of non-drug fits, running is an essential part of the pattern. Oriented running, followed by blind running, as mentioned above in the description of a typical seizure, is essential if the animal is to have a seizure. We have found the maxim "no run, no fit" to hold true. Bound animals cannot run, hence do not experience a convulsive seizure in the presence of auditory stimulation.

As previously mentioned, we cannot explain "audiogenically" the running phenomenon, nor the variability of reactions of the same animal to the same stimulus on different days. The "audiogenic" theory likewise does not afford an explanation of the variability in the pattern of the convulsions. We could hardly assume that the same stimulus acting on the same organism would act so differently from day to day. The above phnomenon, observed by us, could perhaps be explained by assuming that the variability arises from the particular animals' psychological condition, or "affective" tone, on the day of stimulation. On some days, dependent on the rats' general emotional level, it is easier to elicit a fear response, than on others.

The importance of the running phase of the convulsion as well as the beneficial effect of Dilantin (1) in alleviating the seizures, points to functional rather than structural interpretation of the convulsions which we have produced in the white rat. It is not likely that Dilantin is specific for one portion of the nervous system (such as the auditory system). It seems more probable that the drug has a more general effect on the nervous system, perhaps on the emotional mechanisms.

Experiment 1 of our research has indicated that with successive seizures the period of the running phase is diminished. This may be interpreted to indicate a general increase in the emotional tone of the animal which has been repeatedly thrown into convulsions. Such an increased emotionality in turn would render the rat capable of being frightened, to the extent of precipitating a fit, without the necessity of the preliminary running period, which may function to increase emotionality to a level concomitant with a convulsive seizure. We may mention that the reduction of the running period and the increase in time spent in the post-convulsive, or coma-state, in the parent animals enabled us to breed "chronic" animals from them, rats which exhibited abnormal behavior from birth, or shortly thereafter, without the need of stimulation of any type.

Experiment 1 has shown that 50 per cent of our animals had seizures in the presence of a ringing bell. This percentage agrees well with that found by Humphrey and Marcuse (4), but does not support the statement of Maier (7), that of the various types of stimuli used to produce convulsions experimentally, the bell is the least effective. We would agree with Morgan (9) that the auditory stimulation may be of importance in inducing seizures in some animals, but we do not feel that the auditory component the stimulation in and of itself acts as an "audiogenic" "spark-starter" for the convulsion. Rather it is our opinion that auditory stimulation is merely the most effective way of inducing emotionality, or "fear" reactions in the animals. Unless the emotional centers are aroused there will be no seizure, regardless of how long the auditory centers are stimulated. We can agree with Hall (3) that the excessive activity on the part of an animal may be interpreted as a mechanism of protective nature, serving to "blow-off' excess nervous energy, which would otherwise be expended in a convulsive seizure. We cannot support this author in a further supposition that the so-called nervous animals are, in view of the above statement, more resistant to seizures than are the "phlegmatic" rats. Our reasons for disagreement on this latter point will be considered at a later point in this discussion.

Briefly summarizing the facts brought out in Experiment 1 which we feel strongly suggest a functional rather than a structural interpretation of the convulsions produced in this experiment, we would emphasize again:

1. Variability of both seizure patterns and seizures in individual animals.
2. Prolonged stimulation of animals showed that some rats exhibited seizures only after many trials covering many months.
3. Audiogenic theory cannot explain the running phase of convulsive patterns satisfactorily.
4. With auditory stimulation kept constant, manipulation of the environment proved an effective method of reducing the seizures.
5. The non-specific substance Dilantin Sodium was effective in reducing convulsive seizures (1).

With the above factors in mind we offer the following as the best explanation of the convulsions produced by us in Experiment 1. Animals placed in the presence of a ringing bell seek escape from the stimulus, which through excitation of the thalamic and hypothalamic emotional centers produces a fear (or increased emotional) reaction in the rat. This fear-escape reaction manifests itself in running. The running is divisible into oriented and "blind" phases. The tone of an auditory stimulus is important only in so far as it is optimum for producing the fear reaction. If "shelter" is achieved during the oriented stage of the running phase, or if it is experimentally provided, the probability of the animals' having a seizure is reduced. The fact that animals are reported to have a greater proportion of seizures when placed in a confined field is due in all probability to the lack of "shelter" possibilities.

We have made the observation that, although the "shelter" itself is a confined space, animals very seldom have seizures if they seek out the shelter in their oriented state. If, on the other hand, an animal is placed in the confines of a "shelter," and escape blocked, the probability of his having a seizure is increased. We again point out that although physical stimulation of the auditory system under the above two circumstances cannot account for the variation in reactions, the difference in psychological condition, or affective tone of the animal, is very probably the explanatory factor.

Although, as mentioned, the running stage is of paramount importance in the pattern of the non-drug fits obtained by us in Experiment 1, there is still a question as to whether an animal fails to succumb to a convulsion solely because the musculature is inhibited from as great a discharge as a fit warrants. In the case of our binding experiments, some animals exhibited no tension, no struggle to free themselves from the bonds, which were loose enough to allow such a procedure, and which they certainly could have accomplished under pressure of as much muscular discharge as ordinarily accompanies a convulsion. Such animals, when forced out of their bonds to the floor, in the presence of bell stimulation, in some instances have seizures, in others remain quiet and do not have a seizure. We feel that these reactions to binding are explainable, at least in part, in terms of the psychological effect on the animal. The major factor appears to be the kinesthetic sensations which the rat experiences from binding. Such sensations possibly add to a feeling of "shelter" and protection, similar to those experienced by the animal in the tunnels of its native haunts, or by the laboratory animal crouching in an experimental "shelter." We do not feel that rats used in the binding experiment worked off so much energy struggling against the binding procedure that it was unnecessary for them to succumb to a fit in order to relieve the nervous energy. Since, as we have pointed out, the bonds were very loose the animals could have escaped with very little expenditure of energy, and also, since the majority of animals were anesthetized before binding, the explanation of Hall set forth above is not tenable.

We would like to differentiate between the "shelter" reaction which we have found effective in reducing convulsive seizures in animals subjected to auditory stimulation, and the "abortive" jumping reaction developed by Maier (5), as a method of producing similar alleviation of the fits. In Experiment 2 of our research, dealing with the use of the discriminatory problem reaction as a means of inducing seizures in the rat, the animal reported as succumbing to a fit when presented with two negative cards and stimulated with electric shock, jumped clear of the discrimination apparatus and had a convulsive seizure on the floor. This jumping clear of the apparatus was also observed in two other animals who served as subjects in the section of this research titled "Transmission of Convulsions in the White Rat." Such reactions obviously occurred while the animal was still in an oriented condition, else the jumping could not have been properly directed to enable escape from the situation. The actual seizure thus took place on the floor, and not while the animal was in the apparatus proper. The animals then, actually made what Maier would term an "abortive" jump, and yet such a reaction had no effect in alleviating the convulsive seizures which these three animals underwent on the floor. Maier's reports concerning the reactions of his animals to air blasts coupled with negative cards, do not make it clear as to the actual manner in which the animals had seizures in the discrimination problem situation. If his rats reacted as we have described above, then some differentiation must be made between jumps preceding actual convulsive seizures, and the jumping which he has described as "abortive."

If we assume for the moment, as Maier does, that a "conflict" brought about by the presentation of the negative cards in conjunction with an air blast, is the fundamental factor in causing the convulsions, then if we remove the animal, or allow him to physically remove himself from facing the critical situation, he should have no seizures. The reactions of the three animals described above are in direct contrast to such an explanation. On the other hand, were we to open the door of our experimental room (as has actually been done) and allow the animals to physically remove themselves from the presence of the exciting stimulus we should not expect that they would have a seizure (nor did they). We merely wish to emphasize that our animals were not permitted physical escape from the stimulus in the "shelter" reaction experiments; rather they were provided with psychological escape, which we feel constitutes an argument in favor of a functional basis for the convulsions evidenced in the presence of bell stimulation.

Morgan (9) feels that the emphasis on adjustment as a form of response has led to a misinterpretation of the significance of the experimental production of neurosis. This author points out that, in the development of the experimental neurosis, the experimenter discards some rule that the animal has learned. The old rule, according to Morgan, is not changed to any new one that the animal might learn, since, if this were done, the animal would not have an attack. Instead, Morgan states, of a situation in which the animal changes his routine and attempts to find a new set of rules, his behavior becomes erratic and he develops what experimenters have termed a neurosis. Morgan feels that this is a poor term, since in his estimation, the animal has no disease of the nervous system, but is merely thrown into a state of non-adjustment. Commenting on this last statement, we would point out that while the body of the above theory may be sound, our results with breeding experiments and the production of "chronic" animals, stand out strongly in opposition to any supposition that the nervous system of convulsive animals is unaffected by the seizures; whether one wishes to call this effect a disease or not is an open question.

Maier (7) has placed great emphasis on the "conflict" situation, produced by the negative card situation. As a motivating stimulus this investigator used a blast of air. He has claimed that of the two factors, auditory stimulation and discrimination problem, the latter plays the more important rôle in the production of a seizure, being actually indispensable for obtaining the convulsion in some animals. In Experiment 2 of our research we have attempted to duplicate Maier's two negative card situation. We have, however, changed the so called "motivator" from the air-blast to an electric shock, for the purpose of discovering whether the negative card situation actually is as important as Maier would have us believe. As we have reported, one animal out of the 10 subjects used in the negative card situation had a seizure. None of the animals had seizures when the cards were employed in absence of the electric shock. Subsequently in selective breeding experiments we produced two more animals reacting positively to the negative cards plus shock. These animals, however, died before adequate tests could be made on them.

Among those workers placing importance on the "conflict" as being one of the necessary factors for the production of convulions in rats, it seems tacitly assumed that the same reasoning which applies to an animal making discrimination choices likewise applies in the negative card situation. In the discrimination problem procedure the animal is taught a series of reactions and avoidances. He connects an adient response to one card and an abient one to another. He then goes through a series of reactions where the situation confronting him is one of adience and abience. Now when the rat is confronted, in the two window situation, with two negative or abient stimuli, the situation, in our estimation is at once changed. With due respect to Morgans' theory, reported above, it is our opinion that the experimenter has changed the "old rule to a new one," i.e. adient-abient reactions change to abient-abient. This situation has never before confronted the animal. At the point of presentation of the two negative cards we contend that the situation has changed, the psychology of the rat is entirely different. We may even assume that, immediately the two negative cards are presented, the situation is comparable to one in which the rat has been removed from the problem situation tests. The animal was, in these latter mentioned discrimination tests, engaged in actively choosing his reactions in accordance with the stimulation. In the entirely new and different situation brought about by the two negative card test, an external stimulus in the form of an air blast, or shock is introduced. We cannot agree with Maier that such external stimuli are acting to force the animal to solve an unsolvable problem, presented by the two negative cards.

No problem exists when the two negative cards are presented to the rats. As we have reported, the final reaction of animals faced with the negative cards is an abient one, which is correct. It is true that some evidence of emotionality is exhibited in the presence of the two netative stimuli, but certainly is too small to act as much of a factor in the production of a convulsive seizure. The addition of an external agent in the form of a shock or an air blast cannot, we believe, transform a no-problem situation into a problem situation. It is probably true that the shock has the function of substituting maladaptation for adaptation as reported in human studies. Our former statement would not indicate that the external stimulus does not create a new and entirely different problem, concerning which we shall speak presently. We would point out that if there were any serious problem connected with the presentation of the negative cards, in the sense of a "conflict" due to an unsolvable situation animals should precipitate themselves into a fit trying to solve the "impossible," without the need of adding an external stimulus. If this additional agent in the form of shock or air blast is functioning as a motivator, what has happened to the potency of hunger and thirst, used throughout the training periods as motivators? Must we assume that these two ordinarily effective stimuli suddenly become less effective when the animal is presented with the two negative cards?

If the role of the external stimulus, introduced at the point of presentation of the two negative cards, is not that of a motivator, then what function does it perform? In our opinion the shock or the air blast plays the same role as the "senstitizers" used by us in Experiment 3 of this research. The "conflict" if such exists is brought about by the presence of an unpleasant situation, created by the closed field, increased to an unbearable point through addition of an external stimulus in the form of shock or air blast. Thus, the so-called "conflict" is between remaining in an unbearable environment and the possibility of escape from that environment. The problem changes, as we should expect, in as much as the two negative card situation is a change from the original problem where the task confronting the animal was one of making a correct choice in order to obtain the desired reward.

We may summarize our discussion of Experiment 2 in the following manner: the rat faced with two negative cards finds himself in a closed field from which he cannot escape. This very fact may be sufficient to create a certain degree of nervousness in some animals, but entirely insufficient to be of primary importance in producing a convulsive reaction. If an additional agent, in the form of an air blast or an electric shock, is introduced in conjunction with the negative card situation, the emotional level is still further increased, as the result of this added unpleasantness, to the extent that in a few cases convulsions are actually precipitated.

It would seem that, since our experiments have merely substituted a different external stimulus, in conjunction with the negative cards, for the air blast used by Maier in his studies, the percentage of seizures obtained in the two investigations should be somewhat comparable. We have seen that this is not the case. The obvious reason for the discrepancy between Maiers' claims of considerable success with the "conflict" method of producing abnormal behavior, and the fact that our more detailed studies failed to substantiate this claim, returns to the fact mentioned previously that he did not give his experimental animals sufficient preliminary trials to demonstrate conclusively their negativity to the air blast.

In concluding the discussion on "conflict" as a means of producing seizures of a convulsive nature, it seems rather evident that if the external stimulus were acting as Maier has assumed, that is as a motivator, then any potent motivator should, in combination with the negative card situation, produce a comparable percentage of seizures. Especially should this be the case in the event that the "motivation" factor is the less important of the two, as far as the production of convulsions in the rat is concerned. Since our experiments have failed to produce a comparable number of seizures, using the "conflict" method, two possible explanations may be offered. Either the seizures reported by Maier were actually due to the air blast, which as we have previously mentioned, is a possibility, due to failure to separate experimental from convulsive animals on the basis of sufficient trials, or the nature of the construction of our apparatus was such as to inhibit convulsive seizures. As we have pointed out, running, both oriented and "blind," is a definite stage of the convulsive seizure. The animals reacting positively to the negative cards in conjunction with shock jumped free of the apparatus and succumbed to a seizure on the floor. Animals not reacting positively remained in the apparatus. It is possible that, were the apparatus so arranged as to permit running, the number of seizures would have been increased. To our knowledge, Maier's apparatus did not permit this running stage to any greater extent than the one employed in our own experiments.

To obtain acutely disordered behavior in the rat, stimuli of three grades were used by Humphrey and Marcuse (4); one in which an electric bell was rung for 3′ on the floor of a carton, on the top of which an animal was placed; ringing the bell close to the cage and, swinging the cage from side to side along with ringing of the bell in position 2. These investigators found that while the third procedure induced seizures in 50 per cent of the normal male animals, procedure 1 had no effect on 24 male animals and induced seizures in only 26 females. Procedure 1 did induce seizures in 50 per cent of the chronically disordered males. The chronically disordered animals were produced by these authors by a procedure of maze training involving the moving back of the food box in successive trials just as the animals were about to complete their run and enter the box for the reward.

We would point out that these workers have actually done a "sensitizing" experiment similar to the ones which we reported in this research. Previous emotional reactions obtained in the maze situation, although failing to actually produce convulsive seizures, did serve to "sensitize" or increase the general emotional tone of the animals, so that when additional stimuli, in the form of bell ringing, and cage swinging were introduced, convulsive seizures were precipitated. In the other instance, bell ringing plus cage swinging composed the "sensitizing" and precipitating combination. In Experiment 3 of this research, we selected animals of "nervous" temperament (never actually having had a seizure) as indicating the possibility, that since a single stimulus raised the emotional tone to a point at which signs of emotionality were evident, an additional stimulus, having itself the same effect, might in combination with the first stimulus precipitate a seizure. Such a theory justified itself as the results of Experiment 3 have indicated. Likewise, in the case of animals studied by Humphrey and Marcuse, the animals previously excited through the maze situation were the ones reacting positively to a subsequently exciting situation. Phlegmatic animals in our experiments proved so well adjusted as to require doses of metrazol bordering on the convulsive amount, before bell stimulation proved effective in causing a seizure. Of course, as we have previously mentioned, the nervous activity of some animals may prevent them from succumbing to a seizure when a single stimulus is used, but this does not negate the importance of nervousness as an indicator of subsequent convulsive seizures, when the proper stimulus, or combination of stimuli is found.

Recently Maier (8) has presented his eighth publication dealing with abnormal behavior in the rat. In this paper he reports concerning the action of convulsive and sub-convulsive doses of metrazol in production of convulsive seizures in the rat. Referring to the literature offered by this investigator in the general field of abnormal behavior in the rat, we find that the following statements have been made by Maier regarding the action of metrazol:

1. ". . . . effective in creating fits in animals not before reacting positively, because such animals have previously been subjected to drug seizures. Animals not so treated are not so definitely affected by the sub-convulsive doses. . . ."
2. ". . . . the metrazol, as such, acting as a temporary excitant enables animals not before succumbing to fits to do so when their excitation level is raised by metrazol. . . . Seemingly the drug itself and not the actual metrazol seizure is the important factor."
3. ". . . . metrazol has a therapeutic value, presumably lowering the excitation value of the negative card situation."

From these statements it is evident that the true action of the drug is hopelessly confused. This state of affairs arises from the failure in the first instance to separate properly animals into control and experimental groups on the basis of previous extended stimulation. As we have had occasion to mention use of such animals, especially in drug work, would naturally give so many different reactions that any attempted explanation would lead to the hodge-podge of inadequately supported conclusions or suppositions noted above. This condition arises naturally from the use of animals whose previous histories were either not adequately determined or inadequately studied. In the paper under discussion Maier reports concerning the differential reaction of metrazol on three groups of animals. Group 1 consisted of rats from stocks "in which the absence of convulsions was the rule." Groups 2 contained animals from "stocks in which the presence of convulsions was the rule." The rats making up Group 3 were those from the matings of Groups 1 and 2. Maier points out that the outstanding difference between the groups lay in the fact that animals in first two groups had had "previous metrazol experience"; in other words a history of convulsive seizures induced by metrazol; Group 3 had no such experience. Subsequently this author finds that rats of Groups 1 and 2 react positively when given a sub-convulsive dose of metrazol and then subjected to auditory stimulation. The animals of Group 3 give inconclusive results with this same procedure. From this evidence Maier concludes that metrazol convulsions must lower resistance to fits attending auditory stimulation, and further that convulsions evidenced in the presence of auditory stimulation are functional and not structural in nature.

We do not feel that either of the above mentioned conclusions is justified on the basis of the evidence presented by Maier in his eighth publication. The conclusion that previous metrazol convulsions are the potent factors in reducing resistance to auditory stimulation could only have been drawn had no injections of the drug been administered on the day of the critical test with the auditory stimulus. Since, however, metrazol was administered on the test days, our contention, that combinations of ineffective stimuli, one acting as "sensitizer" and the other as "precipitator," caused the convulsions, is borne out by Maier's own results. The fact that small amounts of the drug were effective is of no importance, since one would expect that such would be the case in the event that animals were previously thrown into metrazol convulsions.

From our work we may suggest three reasons which might explain Maier's lack of convincing evidence regarding the action of metrazol on rats not previously subjected to drug seizures. Comparison of the amount of metrazol which Maier has given his animals in Group 3, with table 6 of our research, indicates that he has failed to use sufficient amounts of the drug. This table also indicates that there is a differential reaction on the part of the animals to the drug attendant upon their genetic histories. The last section of table 6, composed of animals which were the offspring of one convulsive and one normal parent, would correspond with rats making up Group 3 in Maier's experiments. It is at once evident, on comparison of animals in section 3 of table 6 with those of the first two sections of the same table, from which they differ only as regards genetic history, that they give the most variable reactions to the drug. This fact would indicate that the variability found by Maier in reactions of animals which were the offspring of one convulsive and one non-convulsive stock had nothing to do with the presence or absence of previous metrazol seizures. The third (and in our estimation the weakest, in the light of the data of table 6) possible explanation of differential reactions of Maier's three groups of animals to metrazol given in sub-convulsive doses would be that authors own interpretation, that Group 3 had no previous metrazol experience.

Regarding the phenomenon of "sensitization" reported by us in Experiment 3 of this paper, it is our feeling that the genetic history of convulsions in the family of the individual rat is the primary factor in explanation of differential reactions to a combination of sub-convulsive doses of metrazol and auditory stimulation. Metrazol, as extraneous noise, and electric shock, used in other of our reported experiments, merely serves as a "sensitizing" agent to increase the animals' emotional threshold, to the point where, when an additional excitant is added (ringing bell) a convulsion is precipitated.

As we have noted, Maier has confused this issue by stating at one point that it is the metrazol itself which is the important factor in causing a seizure in refractory animals; suggesting on the basis of grossly inadequate evidence that the drug may act as a temporary excitant through the sympathetic nervous system. We believe that our work has clearly shown that matrazol given in sub-convulsive doses does act as a "sensitizer," which makes it possible for refractory animals with certain genetic histories to succumb to convulsive seizures in the presence of auditory stimulation. If the drug does act as we have determined it is rather unlikely that it has therapeutic properties regarding the seizures as Maier has claimed in another portion of his research. Our results are likewise clearly in opposition to Maier's insistance that previous metrazol seizures are required in order for sub-convulsive doses of the drug to be effective in producing seizures in refractory animals.

We do not feel that any conclusion can be definitely drawn from the fact that sub-convulsive doses of metrazol are effective, when combined with another exciting agent, in precipitating convulsions in hitherto refractory rats, regarding the structural or functional foundation of convulsions attending auditory stimulation. More complete proof of this fact lies in the demonstration that proper manipulation of the animals' environment, keeping them still in physical contact with the exciting stimulus, is effective in reducing the percentage of seizures experienced. We have presented such evidence based on "shelter" reactions reported in this paper.

SUMMARY AND CONCLUSIONS

The experimental production of convulsions was studied in 120 white and black and white rats over a period of 2 years. The research is divided into 4 major experiments. In Experiment 1, animals were stimulated for a prolonged period with an electric bell. It was found possible to divide subjects into "convulsive" and "normal" only after at least 60 stimulations. Complete division into the above groups was entirely impossible in the case of a few animals even after prolonged test periods. The electric bell proved to be an effective method of inducing seizures in 50 per cent of the original stock. Continued tests over a long period rendered animals less resistant to the bell, as evidenced by a decrease in the length of the stimulation period, and an increase in the post-convulsive period.

Experiment 2 indicated that the so-called "conflict" method of producing convulsions, when not employed in combination with auditory stimulation, was effective in only 10 per cent of the cases. While auditory stimulation is not an essential factor in production of fits by non-drug and non-electrical methods, it is certainly the most effective method.

Experiment 3 indicated that two ineffective stimuli may, in combination, prove effective in producing seizures in resistant rats. The degree of emotionality, as evidenced by reactions to single ineffective stimuli, as well as the genetic histories of the individuals, are primary factors in determining the effectiveness of the "sensitization" or combination of single ineffective stimuli as a means of experimentally inducing convulsions.

Experiment 4 was concerned with psychological and mechanical methods of alleviating seizures produced in the presence of auditory stimulation. Both the "shelter" reaction and the "binding" procedures proved effective as means of reducing the susceptibility to seizures.

Results of the foregoing experiments and observations of animals during the 2-year period over which the research was conducted led to the development and support of a non-audiogenic theory of experimentally induced convulsions in the rat. The theory developed and supported is that the convulsions produced in this study are functional, due to stimulation of the emotional centers, and not structural. Fear and escape are the basic principles underlying the seizures. Certain psychological and mechanical methods of alleviating the convulsions add support to our theory.

From the results of these experiments, more particularly from the success of Dilantin Sodium (1), (2), in alleviating the seizures, we offer the suggestion that the seizures produced and studied in our laboratory are epileptoid reactions precipitated by the emotion of fear.

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